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Primary Carcinoid Tumor of the Liver: Report of Four Resected Cases Including One With Gastrin Production

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Four cases of primary hepatic carcinoid were identified during a retrospective study of liver resections for primary tumor. The cases included two adult males, one adult female, and a 9-year-old boy in whom gastrin levels were documented. The estimation of gastrin levels was prompted by symptoms suggestive of acid-peptic disease. One patient died postoperatively. The other three are alive and well at 3 years, 2 years, and at 1 year, respectively, after surgery, outcomes distinctly different from hepatocellular carcinomas. Diagnostic difficulties may be experienced in histologic assessment, and this may require recourse to immunohistochemistry and electron microscopy. Long-term follow-up and careful exclusion of a possible primary elsewhere are necessary for establishing the primary nature of liver carcinoids. © 1996 Wiley-Liss, Inc.

KEY WORDS: **APUDoma, neuroendocrine tumor, liver, gastrinoma, Zollinger-Ellison syndrome**

INTRODUCTION

The liver is an uncommon site for primary carcinoid tumor. Twenty-nine cases had been reported in the literature until 1991 [1]. Since then, to our knowledge 10 more cases have been reported [2–10]. Only a few of these reported cases have been functioning tumors [2,8,11,12]. Demonstration of the hepatic origin of these tumors may be difficult because the liver is a frequent site for metastasis of carcinoids from the bowel and the pancreas. The problem is further compounded by recent observations wherein neuroendocrine differentiation has been documented in hepatocellular carcinomas (HCC) [13]. However, it is necessary to distinguish between the two entities because of the important differences in the clinical evolution of HCC and primary carcinoids of the liver.

We report here four resected cases of primary carcinoid of the liver that we have seen in this hospital.

MATERIALS AND METHODS

On a review of liver resections for primary tumors over a 16-year period, four cases of primary liver carcinoids were identified. Of these, the initial pathologic diagnosis in one case (case 1) was hepatoma. Relevant clinical information was abstracted from the patients' charts and the histology slides were reviewed.

RESULTS

The clinical features are summarized in Table I. The mean age of the patients was 34.8 years (range 9–50 years). Patient 4 was the only female. The presenting symptoms were nonspecific but suggestive of abdominal disease. None of the patients had symptoms of the carcinoid syndrome. Serum alphafetoprotein levels performed in cases 3 and 4 were normal. Hematologic and biochemical investigations were within normal limits in all patients with the exception of case 2, who was anemic (hemoglobin 4.3 gm%) and had a serum gastrin of 703.6 pg/ml

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TABLE I. Clinical Features of Four Cases of Primary Carcinoid Tumor of the Liver*

Case Age/Sex	Symptoms	Treatment and follow-up	Pathology
1. 50/M	Abdominal swelling and nausea (5 months)	Extended right hepatectomy; Died 2nd postoperative day.	27 × 21 × 8 cm nodular, 2200 gm AFP, Grimelius-negative. Chromogranin-positive.
2. 9/M	Abdominal pain (1 year), melena, hematemesis	Wedge resection of the right lobe; NED—3 years.	6 × 6 cm, mucin, Grimelius, AFP, CEA-negative. Chromogranin, neurone specific enolase-positive.
3. 40/M	Weight loss (1 year), itching, loose motions	Right lobectomy; NED—3 years.	19.5 × 18 × 9.5 cm, 1750 gm, Chromogranin, epithelial membrane antigen-positive; carcinoembryonic antigen, neurone specific enolase, AFP-negative.
4. 40/F	Abdominal pain	Embolisation followed by left lobectomy with caudate lobectomy; NED—1 year.	5 × 4 cm, Grimelius-negative, Chromogranin-positive.

*NED, no evidence of disease.

(normal < 90 pg/ml). When seen 1 year after surgery, his serum gastrin levels had risen to 182 pg/ml after an initial drop to 103 pg/ml. CT scan at this stage, however, failed to show any recurrence. Ultrasonography showed echogenic areas in the liver in all the cases. Hepatic scintiscan done in case 1 showed a large cold area in the lower half of the right lobe and the adjoining left lobe. Patient 2 had undergone an upper gastrointestinal endoscopy elsewhere where esophagitis, duodenal ulcer, and duodenal stenosis were noted. Patient 4 had a fine-needle aspiration of the liver, which was interpreted as a neuroendocrine tumor. An mibg (metiodide benzyl guanidine) scan performed after this for other foci of neural crest tumors was negative. In view of the vascularity of the tumor in patient 4, a preoperative selective hepatic artery embolization was done, which produced 40% tumor regression.

Grossly, the tumors were yellowish and solid-cystic on their cut surface (Fig. 1). They were present in the right lobes in cases 1–3 and affected the caudate as well as the right and left lobes in case 4. Microscopy showed the tumor with a solid insular pattern (cases 1 and 2), a mixed solid and trabecular pattern (case 3) and a microglandular pattern in case 4. Islands of tumor cells were separated by thin, well-vascularized septae, some of which were hyalinized. Peliosis-like areas were seen in case 1. The tumor cells had scanty acidophilic cytoplasm and round, mildly pleomorphic nuclei with stippled chromatin (Fig. 2). Case 4 showed foci of necrosis and occasional tumor emboli in the vessels. Of the two tumors with a tumor capsule (cases 3 and 4), irregular infiltration by tumor was noted in case 3. The surgical margins were involved by tumor in case 1. All four tumors were positive for chromogranin (Fig. 3).

All patients underwent surgery as shown in Table I. Patient 1 had a stormy postoperative period and was re-explored for portal radicle bleeding and diaphragmatic tear and died on the second postoperative day. The other three are alive at 3, 2 and 1 years, respectively.

Electron microscopy was carried out on formalin-fixed

Fig. 1. Slices of liver tumor showing small multiple cysts and areas of hemorrhage (Case 1).

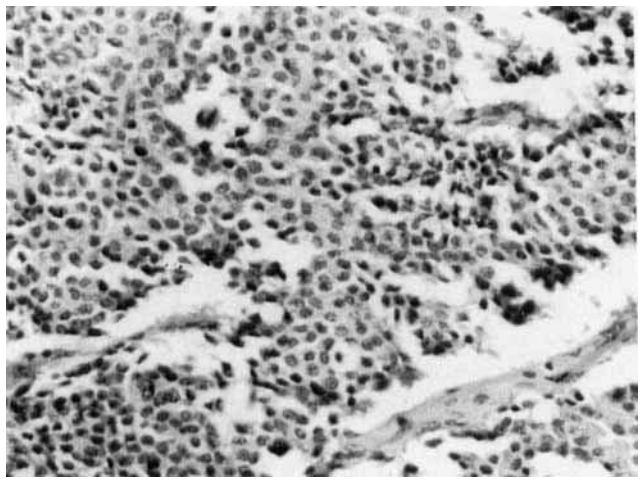

Fig. 2. Typical appearance of carcinoid tumor. Islands of cells are separated by vascularized septa. Note the plasmacytoid appearance of the cells (Case 3) (HE × 200).

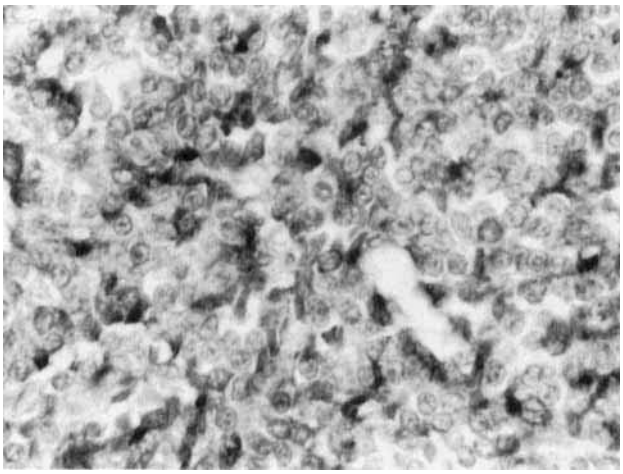

Fig. 3. Microphotograph showing immunohistochemical localization of chromogranin in the tumor cells (400×).

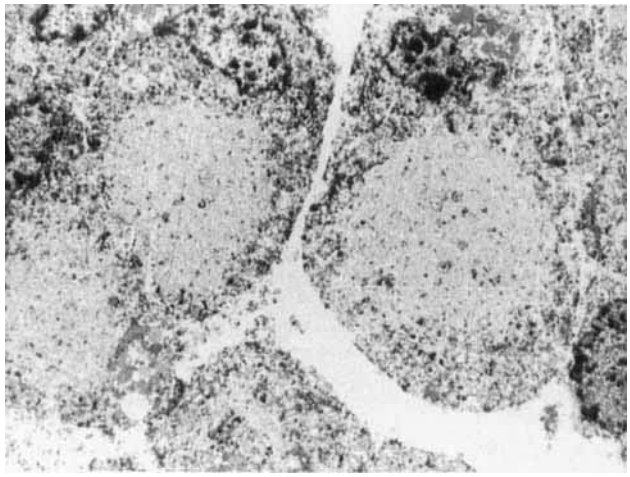

Fig. 4. Electron micrograph (4400 × original magnification) showing eccentric nuclei and central electronlucent zone in the cytoplasm, composed of tangles of intermediate filaments. Note scattered electron-dense neurosecretory granules in this zone. Compressed cytoplasmic organelles are seen at the periphery.

material in case 3 and showed polygonal tumor cells with few cell junctions. The nuclei were eccentric and oval and had a few small chromatin clumps. The cytoplasm showed central rounded electron-lucent zone surrounded by an electron-dense area. Electron-lucency was due to presence of whorls of intermediate filaments (Fig. 4). Dense-core, membrane-bound neurosecretory granules were seen mainly in this filamentary zone. Electron density was attributed to the condensation of organelles. In the cells without filaments, the neurosecretory granules were clustered near the cell membrane. Lipid droplets were also seen. The histology slides from this case were also reviewed and the diagnosis confirmed by the Divison of Hepatic Pathology of the Armed Forces Institute of Pathology (Washington, D.C.).

DISCUSSION

Primary carcinoids of the liver are uncommon neoplasms. The increasing use of immunohistochemistry in routine surgical pathology practice has led to a better understanding of histogenesis of liver neoplasms and, consequently, of recognition of these tumors. Identification of these tumors is important because most of them are of low grade malignancy, unlike HCCs. Clinical suspicion is unlikely because most cases present with hepatomegaly. Zollinger-Ellison syndrome similar to our case 2 has been reported before [2,8]. Three of our patients were males, including a 9-year-old child. This is in contrast to reports in the literature where most cases have been described in women [1–4,7,10–12,14]. There is only one reported case of hepatic carcinoid in a child [8].

Serum alphafetoprotein levels are usually raised in HCC and are useful in the diagnosis. However, absence of raised serum alphafetoprotein does not exclude the diagnosis of HCC. In a comparative study of ultrasound, CT, MRI, and angiography, it has been suggested that multiple small cystic areas may be characteristic of liver cell carcinoids [1]. However, imaging does not distinguish primary from metastatic carcinoids. Further, details of imaging are not available in all the reported cases. The majority of the cases were diagnosed after surgical resections. Most tumors were large and mainly solid in consistency. Only a few were partly or entirely cystic [1,2,6,9,10]. In one autopsied case, the diagnosis was revised to carcinoid from an earlier report of small cell carcinoma made during life [11]. A chance observation made at electron microscopy enabled the diagnosis in a case reported by Norgaard and Bardram [15]. Histologically, carcinoids show a variety of patterns viz. insular, trabecular, gyriform, tubular, and mixed. Reported cases of liver carcinoids have shown all these patterns. In our cases, the predominant pattern was insular.

The diagnosis is usually straightforward when the pattern is typical. However, distinction between hepatic carcinoids and HCC may be difficult [15], as was experienced in one of our cases (case 1). HCC usually shows large polyhedral cells. Presence of sinusoidal investment, trabecular arrangement, bile production, and canalicular differentiation are some of the diagnostic features of HCC. However, small cell variants of HCC and large cell variants of carcinoids may pose diagnostic problems. The histochemical workup of carcinoids usually involves demonstration of argyrophilia and argentaffinity. These were not observed in any of our cases. However, it has been pointed out that foregut carcinoids are not consistently argyrophilic [16].

A variety of immunohistochemical stains have been performed on liver carcinoids. Chromogranin, synapto-

physin, and neurone-specific enolase are the usual markers in identifying cells of APUD origin. Chromogranin has a high degree of sensitivity for APUD tumors. All our cases showed positivity with chromogranin. Specific markers for hormone production have shown a variety of secretory products in primary carcinoids, including gastrin, pancreatic polypeptide, vasointestinal polypeptide, calcitonin, parathormone, ACTH, serotonin, insulin, and somatostatin [2,5,8,10,12,14,15,17]. In one of our cases (case 2), serum gastrin levels were elevated, although no immunohistochemical confirmation could be made. The fact that serum gastrin level dropped initially after surgery indicated that the liver carcinoid was the likely source. Membrane-bound neurosecretory granules are diagnostic of apudomas at electron microscopy. Electron microscopy is also helpful in excluding HCC and cholangiocarcinoma. Filamentous cytoplasmic inclusions have been reported earlier in many apudomas, including pancreatic polypeptide-producing apudoma of the liver [17]. Tumors in which a carcinoid pattern is seen along with HCC or cholangiocarcinoma strictly do not belong to the category of tumors reported here. Neuroendocrine differentiation has been observed in otherwise typical hepatomas [13].

Endocrine cells have been demonstrated in the epithelium of the extrahepatic biliary tree and are believed to be the source of carcinoids in the biliary tree [18]. It is reasonable to assume that primary liver carcinoids arise from endocrine cells in the intrahepatic biliary tree. In fact, human reactive bile ductules have been shown to display neuroendocrine features [19].

Recognition of these neoplasms is not only of academic interest, but also of clinical importance. Unlike HCC, where the prognosis of the patient is dismal, long-term survival has been documented in many patients with hepatic carcinoids, including three of our own cases.

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